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# LIFE COURSE DETERMINANTS OF WOMEN'S HEALTH: FROM REPRODUCTIVE AGE TO MENOPAUSE

Menghan Gao

高梦晗


Karolinska Institutet

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# Life Course Determinants of Women's Health: From Reproductive Age to Menopause

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

**Menghan Gao**

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*Principal Supervisor:*
Professor Ilona Koupil
Stockholm University
Department of Public Health Sciences

*Co-supervisor(s):*
Professor Peter Allebeck
Karolinska Institutet
Department of Global Public Health

Associate Professor Daniel Falkstedt
Karolinska Institutet
Institute of Environmental Medicine

Professor Gita D. Mishra
University of Queensland
School of Public Health

*Opponent:*
Professor Gunilla Sydsjö
Linköping University
Department of Biomedical and Clinical Sciences

*Examination Board:*
Associate Professor Olof Stephansson
Karolinska Institutet
Department of Medicine

Professor Alkistis Skalkidou
Uppsala University
Department of Women's and Children's Health

Associate Professor Arvid Sjölander
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

# ABSTRACT

Over the past four decades, growing evidence has indicated that characteristics such as birth weight and length of gestation are not only key indicators for infant's health, but also predictors of adult health and disease risk. These findings lend support to the developmental origins of health and disease theory. However, evidence remains inconclusive in terms of female hormone-related disorders, including endometriosis and perimenopausal disorders. Also, little is known about the social patterning of these female health burdens from population-based studies. Furthermore, the psychological health of women with endometriosis has not been adequately explored in longitudinal studies.

Based on identified knowledge gaps and taking advantage of Swedish high-quality population-based registers, this thesis aims to study how factors operating during early life, such as parental and birth characteristics, adult socioeconomic and reproductive factors are associated with subsequent risks of endometriosis and perimenopausal disorders. Further, it explores whether women with endometriosis have higher risk of psychiatric comorbidity.

Study I explored the associations of early life social and health characteristics with risk of endometriosis in a cohort of the second generation of women from the Uppsala Birth Cohort Multigenerational Study. Lower birth weight-for-gestational age, fewer births, and previous infertility disorder were found to be associated with an increased risk of endometriosis. Nevertheless, the inverse association between low birth weight-for-gestational age and endometriosis could not be explained by women's lower number of live births in adulthood.

Study II replicated the original findings in Study I in a nationwide population-based cohort of females born in Sweden between 1973 and 1987. This study confirmed the inverse association between fetal growth rate and risk of endometriosis, and expanded Study I by showing associations of maternal smoking during pregnancy and lower maternal education with endometriosis risk in early to mid-adulthood. The study also found a part of the association between maternal smoking and risk of early-onset of endometriosis was due to slow fetal growth.

Study III focused on the psychological health of women with endometriosis by assessing the bi-directional associations of endometriosis with all psychiatric disorders, as well as the role of familial confounding, in a nationwide cohort of all women born in Sweden in 1973-1990. Statistically significant bi-directional associations were found for endometriosis with many different types of psychiatric disorders, including affective psychotic disorders, depressive, anxiety and stress-related disorders, eating disorders, alcohol/drug dependence, personality disorders, and attention-deficit hyperactivity disorder. These bi-directional associations observed at the population level largely remained in comparisons between exposed and unexposed sisters, suggesting that shared familial liability may not fully explain these associations.

Study IV investigated the developmental origins of three subtypes of perimenopausal disorders using the same cohort as Study I. Positive association between birth weight and a clinical diagnosis of menopausal and climacteric states was found. Higher risk of being diagnosed with other perimenopausal disorders (e.g., atrophic vaginitis) was observed among women born with shorter gestational age. This study also documented that women with higher parental and own educational level in adulthood were more likely to be diagnosed with perimenopausal disorders.

Taken together, this thesis supports the developmental origins of two important female hormone-related disorders during reproductive age and menopause, namely endometriosis and perimenopausal disorders. Our findings highlight the importance of intrauterine environment in shaping the developmental adaptations of metabolism and organ function. In addition to the developmental origins, these female health burdens were associated with a range of socioeconomic and reproductive factors as well as mental health in earlier life. It is therefore important to take a life-course perspective for a greater understanding of the etiology of hormone-related health outcomes and consider potential targeting of the high-risk groups for earlier public health intervention.

# LIST OF SCIENTIFIC PAPERS

I. Gao M, Allebeck P, Mishra GD, Koupil I. Developmental origins of endometriosis: a Swedish cohort study. *Journal of Epidemiology and Community Health.* 2019;73(4):353-359.

II. Gao M, Scott K, Koupil I. Associations of perinatal characteristics with endometriosis: a nationwide birth cohort study. *International Journal of Epidemiology*. 2020;49(2):537-547.

III. Gao M, Koupil I, Sjöqvist H, Karlsson H, Lalitkumar S, Dalman C, Kosidou K. Psychiatric comorbidity among women with endometriosis: nationwide cohort study in Sweden. *American Journal of Obstetrics & Gynecology*. 2020;223(3):415.e1-415.e16.

IV. Gao M, Goodman A, Mishra GD, Koupil I. Associations of birth characteristics with perimenopausal disorders: a prospective cohort study. *Journal of Developmental Origins of Health and Disease*. 2019;10(2):246-252.

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADHD | Attention-deficit hyperactivity disorder |
| ASD | Autism spectrum disorder |
| BMI | Body mass index |
| CI | Confidence interval |
| DOHaD | Developmental origins of health and disease |
| HR | Hazard ratio |
| ICD | International Classification of Diseases |
| IR | Incidence rate |
| LISA | Longitudinal integrated database for health insurance and labour market studies |
| MBR | Medical Birth Register |
| MGR | Multi-Generation Register |
| NPR | National Patient Register |
| PD | Perimenopausal disorder |
| PS | Psychiatry Sweden |
| SE | Standard error |
| SEP | Socioeconomic position |
| SIP | Swedish Interdisciplinary Panel |
| TPR | Total Population Register |
| UBCoS Multigen | Uppsala Birth Cohort Multigenerational Study |

# 1 INTRODUCTION

Endometriosis is a chronic estrogen-dependent inflammatory condition commonly manifest among women of reproductive age.[1] It is characterized by the ectopic presence of endometrial tissue (e.g., glands and stroma) outside its usual physiological site.[2] As signs for the final stage of women's reproductive life, perimenopausal disorders (PDs) are a group of symptoms induced by the variations in reproductive hormone levels or gynecological lesions, occurring during and after menopause, frequently including a range of vasomotor, psychological, somatic and vaginal symptoms.[3-6] Both disorders are highly prevalent and associated with a range of adverse physiological and psychological consequences, which could directly threaten women's health-related quality of life, and indirectly bring significant burdens to the healthcare system and society.[7-12] Apart from established genetic susceptibility,[6,13] the etiology of these disorders (including their potential developmental origins) that could provide important clues for reducing these health burdens, remains unclear.

The developmental origins of health and disease (DOHaD) theory was built upon the well-known "fetal origins of adult disease" hypothesis, which was proposed by Professor David Barker and colleagues to describe the associations between intrauterine environmental exposures and risk of chronic diseases in adult life.[14,15] In light of the DOHaD theory, recent research demonstrates that in addition to genetic impact, human body is in constant developmental changes and makes adaptations to many modifiable factors, such as intrauterine environment or nutrient supply.[14,16] This programming effect may particularly apply to hormone-driven disorders, considering the permanent impact from changes in prenatal endocrine status and hormonal environment on hormone secretion and tissue-specific hormone susceptibility across the life course.[17] It is therefore needed to explore the potential developmental mechanism of factors operating during perinatal and earlier life in contribution to adult hormone-related disorders.

Despite emerging research interest in the intrauterine programming of endometriosis, to date, evidence has been conflicting and inconclusive.[18-22] Findings regarding the association between in utero exposure to maternal smoking and risk of endometriosis are also complex.[18,21-24] These discrepancies in the existing literature may result from low statistical power and usage of retrospectively self-reported information on perinatal characteristics in many of the earlier studies.[18,21-24] Additionally, it is worthwhile to explore the socioeconomic inequalities in endometriosis in population-based cohorts from a country with egalitarian healthcare system.

Although it has been documented that women with endometriosis suffer from worse mental health, such as anxiety and depressive disorders,[25,26] the temporal sequence between these disorders as well as the mechanism underlying them remain unclear. Moreover, it is still unknown whether there is comorbidity between endometriosis and a broader spectrum of psychiatric disorders, such as alcohol or drug dependence disorders, personality disorders, and attention-deficit/hyperactivity disorder. Thus, research is warranted that attempts to

disentangle the bi-directional association between endometriosis and mental disorders across the life course.

With regard to the significant health burden in women's midlife, previous studies have suggested that there might be developmental origins of ovarian aging, given that a positive association was found between birth weight and earlier age at menopause.[27,28] However, whether birth characteristics are associated with the occurrence of clinically diagnosed PDs is not clear yet.

This thesis, therefore, focuses on the developmental origins of important female hormone-related disorders during the reproductive period and menopause, namely endometriosis and PDs, as well as their associations with socioeconomic factors and psychiatric comorbidities across the life course. We hope our findings may shed further light on the etiology of these important disorders burdening women, as well as help to identify the groups of women who are particularly at risk to be benefited from preventive interventions.

# 2 LITERATURE REVIEW

## 2.1 THEORETICAL BACKGROUND

### 2.1.1 A life course approach to health

As defined by Ben-Shlomo and Kuh, the life course approach explores the associations of physical or/and social exposures operating during gestation, childhood, adolescence, and adult life with subsequent heath and disease risk in later life or across generations.[29] It also focuses on investigating the underlying interrelationship between biological, behavioral and psychosocial pathways that contribute to the life course associations between early life exposures and adult health outcomes.[30]

Besides focusing on individuals' life spans, the life course approach additionally puts an emphasis on the intergenerational effects.[30] A frequently studied topic is the effect of maternal health behaviors during pregnancy on health outcomes in offspring. For instance, maternal smoking during pregnancy has been linked to both short-term and long-term adverse health consequences in offspring, such as lower birth weight,[31,32] attention-deficit hyperactivity disorder,[33,34] cardiovascular disease,[35] and respiratory disease.[36,37] The application of a life course perspective in exploring the intergenerational biological and social exposures may help to understand how they contribute to the reproduced ill-health across several generations.

A thorough investigation of the temporal relationship of different biological, psychological, and social exposures across the life course is another important aspect in life course epidemiology. The association between an early life exposure and adult health outcome could be confounded by many factors prior to the examined exposure. Ben-Shlomo and colleagues have advocated that such confounding bias can be largely eliminated through family-based designs, which could also help infer causality in a life course association.[29] Therefore, disentangling the role of confounding underlying any observed association is a priority aim of this thesis.

Furthermore, the life course perspective considers the timing of an exposure as a key contributing factor to health inequalities. For example, if an exposure can only exert a risk effect on subsequent health within a certain time window, then the time window is defined as the critical period.[29] A classic example is the effect of maternal intrauterine undernutrition on offspring's health. Based on the Dutch Hunger Winter Families study,[38] prenatal exposure to famine particularly during early gestation was associated with obesity and breast cancer in offspring. By contrast, exposure to famine during late gestation was associated with a decreased risk of obesity in adulthood.[39] Such findings also suggest that the effect of stimuli or insults during the critical period of life may have long-term influence on health and may not be reversible.

With regard to the timing of exposures, the life course approach also highlights the need for investigation of the underlying causal pathways. For example, the life course chain of risk additive model describes a situation where each exposure could increase disease risk independently, meanwhile these exposures are temporally and causally linked with each other.[29] In light of this, the current thesis also aims to disentangle the direct effect of an exposure from its total effect on certain disease risk, as well as explore indirect pathway of the respective intermediate exposure, which can further illustrate the disease mechanism.

Adopting a life course approach is particularly important with respect to women's health. Women's health can specifically be affected by their reproductive careers or behaviors, such as number of pregnancies, age at first and last birth, and health behaviors during pregnancy, which can be determined by a hierarchy of socioeconomic, environmental, and cultural circumstances. To this end, circumstances around pregnancy and childbirth are important in the life course of women as well as for their offspring's health.

### 2.1.2 The developmental origins of health and disease theory

The developmental origins of health and disease (DOHaD) theory resonates with and is an important part of life course epidemiology.[40] The DOHaD thoery originates from the "fetal origins of adult disease" hypothesis, which was proposed by Professor David Barker and colleagues to describe their findings on the associations between birth weight and increased risks of certain adult diseases, such as coronary heart disease, type 2 diabetes, stroke and hypertension.[14,15,41] The hypothesis proposes that a stimulus or insult acting during the critical or sensitive period of life could exert a long-term permanent impact on body structure, function and metabolism.[17] Considering the critical period in utero for most organs' and systems' programming, the hypothesis has often been referred as the "fetal programming" hypothesis.[42]

The biological basis behind the hypothesis is related to the developmental plasticity of human body. As such, the hypothesis highlights the importance of nutrition during the fetal stage or infancy in shaping the developmental adaptations across the life course, which in turn could affect adult biological outcomes. According to Barker, plasticity during the in utero period allows humans to make short-term adaptations according to their perceived maternal nutritional or hormonal signals.[14] These adaptations are predictions and preparations for future environment.[43] For example, if an infant was exposed to undernutrition in utero, he or she will likely have a decreased body size and altered metabolism to adapt to the forthcoming deprived environment in postnatal life.[14] Fetal growth rate is thus generally believed to be an indicator for fetal nutrition and environment.

Barker and colleagues describe the result of fetal growth restriction or low birth weight as an undernourished fetus's "thrifty" way of survival through mechanism of insulin resistance.[14] This developmental process has been named as a "thrifty phenotype".[44] The thrifty phenotype will increase infant's chance of survival in nutritionally constrained prenatal and postnatal environments. The mismatch between e.g., placental nutrient supply and fetal nutrient

demand will trigger fetal protective mechanism through a series of physiological or genetic adaptations.[17] Issues will however come up when there is another mismatch between intrauterine and postnatal environments, usually deficient intrauterine environment does not predict similar milieu postnatally.[43] Under such mismatched condition, the thrifty phenotype can be a disadvantage for later development and survival, and increases susceptibility to several adverse health outcomes, such as metabolic syndrome or heart diseases.[44,45]

The fetal origins hypothesis has been later expanded to the DOHaD theory to further illustrate the impact of nutritional, hormonal and metabolic environments in utero and continuously through early life development on adult health,[42,46,47] as well as to identify potential modifiable factors across the life course.

### 2.1.3 Social determinants of health

Apart from biological influences, individual's health is also determined by a range of socioeconomic circumstances, such as social support, social network, living and working conditions, as well as general socioeconomic and cultural environments.[48] All these social determinants are embedded in the social context in which individuals live, develop, and age, and will shape one's health directly or indirectly by influencing health-related factors. These include lifestyle, health awareness, behaviors, and knowledge, as well as material resources or ability to access to healthcare. Individual's position in the social spectrum will determine one's vulnerability to ill-health through a chain of influences from a hierarchy of socioeconomic circumstances. At the population level, social determinants of health will become apparent as health inequalities or social gradients in health.

Concomitantly, a main objective of life course research is to clarify the underlying biological, behavioral and socioeconomic processes that contribute to the relationship between certain exposure and outcome within one's lifetime or across generations.[49] To this end, this thesis also focuses on understanding how socioeconomic circumstances across the life course may affect women's health in adult life, and their indirect influences through interacting with other biological or psychological factors.

## 2.2 ENDOMETRIOSIS

Endometriosis is an estrogen-dependent, chronic gynecological disorder commonly found among women of reproductive age.[1] It is characterized by the abnormal presence of endometrial-like tissue (i.e., glands and stroma) from its usual physiological site.[2] Endometriosis is commonly found on the pelvic peritoneum, but could also occur for example, in the ovaries, fallopian tubes, intestine, or rectovaginal septum.[9] A special case of endometriosis is when the detached endometrial tissue moved from the endometrium layer to other parts of the uterus, usually to the myometrium layer.[50] This condition is also referred to as uterine adenomyosis.

### 2.2.1 Epidemiology

There is no general agreement on the prevalence of endometriosis, which varies between 1.3 and 5% among reproductive-aged women according to population-based studies,[8,51-53] while it approaches 6-10% in hospital-based studies.[1] Potential cause for the variations in reported prevalence is that women with pathophysiological signs of endometriosis could experience different degrees of symptoms, some may even have no symptom and therefore do not seek medical care. It is estimated that around 11% of all women could have undiagnosed endometriosis.[54] Apart from that, women with endometriosis may experience serious diagnostic delay, studies have shown that the lag time between onset of symptoms and a definitive diagnosis ranges from 4 to 10 years.[55,56] Also, the diagnostic criteria for endometriosis vary from time to time and differ between countries. For example, although laparoscopy has been referred to as the only reliable diagnostic test to confirm endometriosis,[57] it is not a requirement for endometriosis diagnosis in every country, take Sweden for instance. Nonetheless, study has estimated that around 80% of endometriosis cases recorded in the Swedish inpatient register were histologically confirmed.[58]

### 2.2.2 Etiology

Though the pathologic description of endometriosis was first introduced in 1860,[59] the etiology of endometriosis is still poorly known. Several theories have been proposed to reveal the pathogenesis of endometriosis, the most accepted and convincing one is the retrograde menstruation/implantation theory.[60,61] According to the theory a prerequisite for the development of endometriosis is menstrual reflux, i.e., during menstruation viable endometrial fragments are retrograded through the fallopian tubes and implanted in the peritoneal cavity.[1,62] Apart from that, other sufficient conditions have to be met, which involve immune dysfunction, inflammatory response and incapacity of cleaning the implants (i.e., lesions).[60]

Genetic variant has been shown in recent twin and genome-wide association studies to contribute to endometriosis, which may account for 51% of the variance in liability.[13,63] Apart from genetic origins, the development and establishment of endometriosis also require multiple mechanisms operating throughout the life course, including immune system dysfunction, molecular alterations, metabolism and hormonal regulations.[52,64] Thus, it is reasonable to assume that the disorder is a complex outcome of gene-by-environment interactions in different life stages, which may start already from prenatal period.

### 2.2.3 Developmental origins of endometriosis

#### Birth weight and gestational age

There is no general agreement on the developmental origins of endometriosis. Previous evidence regarding the associations of birth characteristics with risk of endometriosis is inconsistent and debatable. Some studies have provided evidence of the development origins of endometriosis. In a case-control study by Vannuccini and colleagues,[18] they found that

women with endometriosis (n=161) were more likely to be born with low birth weight and prematurely compared to the control group (n=230) of women who undergo laparoscopy but not endometriosis related. However, in this study birth characteristics were only retrospectively collected through self-reported questionnaires, thus recall bias cannot be ruled out. Another case-control study based on 368 women with endometriosis and 375 patients without showed that lower birth weight was associated with endometriosis.[19] An advantage of this study is that birth weights were obtained from medical records, but information on women's gestational age was not available, which limits their ability to investigate whether the negative effect from low birth weight on endometriosis is caused by intrauterine growth restriction or through preterm birth.

In line with these studies, a large population-based cohort study of U.S. nurses showed that the incidence of endometriosis diagnosis was higher among women with lower birth weight, and it was not due to premature birth or multiple fetal gestation.[20] However, both birth weight and incidence of endometriosis were based on self-reported information, as such, birth weight was only investigated in broad pre-specified categories and time for endometriosis diagnosis was unclear.

There are, nevertheless, many studies which failed to find evidence of the relationship between in utero exposures and later risk of endometriosis.[21, 22,24] For example, in a case-control study of 91 endometriosis patients and 82 controls, none of the tested in utero exposures including birth weight showed significant association with endometriosis.[21] Interestingly, this study has similar study design and sample as the study mentioned before by Vannuccini and colleagues, which reported an inverse association between birth weight and endometriosis.[18]

The inconsistency perhaps results from the reliance on self-reported information on perinatal factors, as such findings of these observational studies presumably suffered from recall bias considering the long-term gap between in utero exposures and adult endometriosis. Taken together, there is no firm conclusion on the developmental origins of endometriosis, particularly as many previous studies have methodologic drawbacks, such as self-reported birth information, small samples, and cross-sectional design.

**Maternal smoking**

Exposure to an environmental insult during the critical period of life is believed to bring a potential negative impact on fetal growth and development, which in turn could permanently programme adult health.[17] Studies linking maternal smoking and adult onset of endometriosis are scanty and yielded conflicting evidence. An Italian case-control study found that mothers of endometriosis patients were more likely to smoke during pregnancy, which suggests a risk effect from the hazards of tobacco on the development of endometriosis.[18] By contrast, a cohort study showed that in utero exposure to cigarette smoking was associated with a decreased risk of endometriosis, and the inverse association remained given the absence of current smoking.[23] This finding is however debatable due to the small sample, self-reported

maternal smoking behavior, and residual confounding. Likewise, there are two case-control studies (91 and 310 cases, respectively)[21,22] and one matched cohort study (190 cases)[24] that found no association between maternal smoking and endometriosis risk.

Nonetheless, earlier studies in animals and humans have shown that exposure to dioxin was associated with elevated risk of endometriosis because of the impaired immune function.[65,66] It thus reasonable to hypothesize that there might be an adverse effect from exposure to dioxin and other toxic components from cigarettes in utero. Taking advantage of the Swedish national registers with prospective data on maternal smoking and endometriosis, this thesis aims to reinvestigate this important aspect of the developmental origins of endometriosis.

### 2.2.4 Social and health determinants of endometriosis

#### Sociodemographic factors

Some earlier studies from North America have shown that incidence of endometriosis was higher among women with higher educational level.[67,68] By contrast, findings from the Nordic countries did not show any associations of endometriosis with women's adult education or income.[51,69]

Regarding the association between endometriosis and country of origin, an U.S. study among parous women has found that endometriosis was more prevalent among women with Asian origin compared to Caucasian women.[70] However, this finding was not replicated in the Nurses' Health Study II, a large cohort study also from the U.S.[71] Further, a Swedish study has shown that women who came from Asian countries were at elevated risk of hospitalization for endometriosis compared to Swedish-born women.[72] In addition to possible biological differences, potential underlying causes for the association between country of origin and endometriosis are presumably multifactorial. In this thesis, we are interested in testing the association with endometriosis by using mother's country of origin.

Older maternal age at birth has been suggested to be associated with a decreased risk of endometriosis in a prospective cohort study of French women,[73] while no association was detected in another case-control study.[21] Association of maternal reproductive related factors with daughter's endometriosis may not exhibit a causal relationship but rather explained by unmeasured confounders, such as maternal endometriosis or mental health.[51,74] Thus family-based designs with ability to account for shared genetic and familial environmental factors are required to evaluate the robustness of evidence, which is also an important aim of this thesis.

#### Reproductive history

There is consistent evidence showing that endometriosis is inversely associated with number of pregnancies.[51,68,75,76] In addition, history of infertility was also consistently found associated with higher risk of endometriosis.[51,67] These results point in the same direction as the proposed retrograde menstruation theory of endometriosis (described in section 2.2.2).

However, age at first or last birth was less associated with risk of endometriosis.[51,75] In contrast to endometriosis outside the uterus, uterine adenomyosis (i.e., a special condition of endometriosis where the endometrial tissue abnormally located within the myometrial layer of the uterus) is more likely to be found among multiparous women.[76 77]

**Endometriosis and mental disorders**

From a life course perspective, the risk of a disease is affected by a range of biological, behavioral and psychosocial processes operating across individuals' life spans.[29] Thus, beyond the influence from "fetal programming", the onset and progression of a chronic disease in adult life could also be affected by previous behaviors, physical and psychological health.[49] Because of the nature of endometriosis, such as chronic inflammatory state, incurable condition, adverse consequences on reproductive and physical health, endometriosis has been frequently linked to impaired psychosocial well-being and decreased health-related quality of life among women with the disorder.[10,78] As such, recent review studies have explored the role of psychological factors in the progression and management of endometriosis.[25,26] These studies showed that women with endometriosis are at increased risk of psychiatric disturbances, such as anxiety and depressive disorders. On the other hand, these psychiatric profiles may affect the severity of endometriosis symptoms, for example, through amplifying perceived pain.

Nevertheless, studies regarding the associations of endometriosis with anxiety and depressive disorders were mainly based on small samples (range, 14-166 cases).[25,26] Additionally, firm conclusions are precluded due to common methodologic limitations embedded in these studies, including retrospective and cross-sectional designs,[79-81] residual confounding,[82] and unclear timing of onset or diagnosis of the disorders.[83-85] Only one population-based study so far has assessed the prospective association between diagnoses of endometriosis and mood disorders, but study subjects were only followed for two years, which is too short to fully disentangle the temporal association between these disorders.[82]

Furthermore, the potential association between endometriosis and bipolar disorder has been suggested since the late 1980s.[86] But evidence so far is inconsistent and mainly based on small clinical studies.[86-88] These studies along with other clinical observations, however, suggest that there might be a broader comorbidity between endometriosis and mental disorders,[79,86,89] while, no population-based study so far has explored the associations of endometriosis with all mental disorders while taking the timing of the diagnoses into account.

Considering the heritable nature of endometriosis and mental disorders, any observed associations between these disorders might be spurious as they could be explained by unmeasured confounding factors, such as genetic susceptibility and other environmental factors. Thus, family-based designs by e.g., comparing the risk of a psychiatric disorder between biological sisters with and without endometriosis may help reveal part of the underlying mechanism from, for example, family liability.

## 2.3 PERIMENOPAUSAL DISORDERS

Perimenopausal disorders (PDs) are a group of bothersome symptoms found in women's mid to late adult life, marking for the end of the reproductive period. Symptoms of PD include vasomotor, psychological, somatic, and vaginal symptoms.[5,6,90] Potential causes of these symptoms are genetic susceptibility, variations in reproductive hormone levels, lost ovarian function, and gynecological lesions.[3,4,6] The International Classification of Diseases defines PDs into three main subtypes: menopausal and climacteric states (e.g., hot flushes, sleeplessness, poor concentration, associated with menopause); perimenopausal bleeding (i.e., abnormal vaginal bleeding during peri- and postmenopausal period) and other PDs (e.g., senile vaginitis). It is estimated that around 80% of postmenopausal women have experienced PDs, while approximately 10% of women with symptoms need to seek health care and potentially get diagnosed and treated.[91]

Earlier studies on the predictors for the occurrence or severity of PDs were mainly focused on adult factors. Consistent evidence suggests that smoking,[92-97] alcohol consumption,[93,96] less physical activity,[92-94] menopausal status,[90,92,95,98] mental illness,[92,93,95] and low socioeconomic positions[90,92-94,96] are risk factors for perimenopausal symptoms/disorders. Findings on the association between adult weight/body mass index and menopausal symptoms are mixed. This inconsistency is mainly driven by the variation in study subjects' menopausal status in different studies.[99,100]

The developmental origins of menopause-related disorders were only assessed with regard to age at menopause. Some studies found that higher birth weight or extremes of birth weight were associated with earlier menopause,[27,28] which suggests developmental origins of ovarian ageing. Nevertheless, no study so far has explored the effect of birth characteristics on the occurrence of symptoms/disorders in perimenopausal period. The lack of investigation may partially be due to few existing longitudinal data sources containing prospective information on both birth characteristics and menopause-related health outcomes.

# 3 AIM AND RESEARCH QUESTIONS

This thesis applies the life course perspective to explore the developmental origins and the social determinants of ill-health among women. The overarching aim is to investigate a range of early life physiological, socioeconomic, demographic, and mental exposures of major female hormone-related disorders during reproductive period and menopause, namely, endometriosis and perimenopausal disorders (PDs).

The specific research questions for each study included in the thesis are:

I: To explore the associations of birth characteristics as well as parental and adult socioeconomic and reproductive factors with endometriosis. (Study I)

II: To explore the perinatal determinants of endometriosis, with specific focus on maternal and birth characteristics. (Study II)

III: To investigate the bi-directional associations of endometriosis with a broad spectrum of psychiatric disorders, as well as the role of familial confounding. (Study III)

IV: To investigate the developmental origins of three subtypes of PDs, including menopausal and climacteric states, perimenopausal bleeding, and other PDs (e.g., atrophic vaginitis). (Study IV)

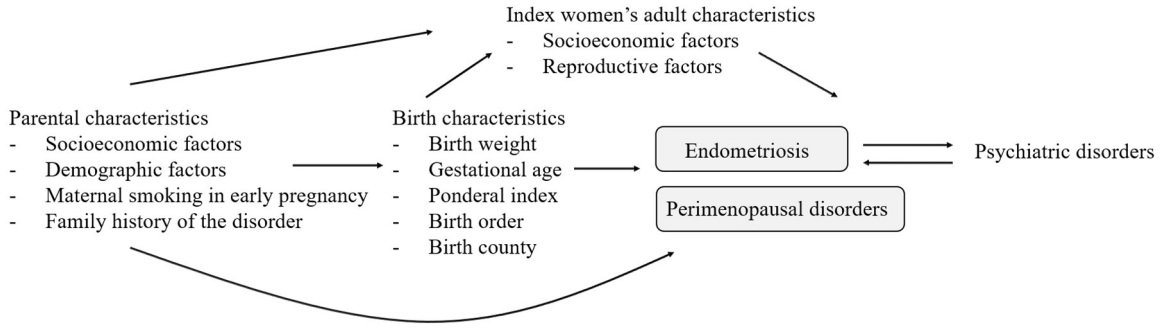


**Figure 3.** Conceptual diagram.

# 4 DATA SOURCE AND MEASURES

This thesis is based on three register-based longitudinal studies created by linkage of routinely collected population-based registers, containing demographic, socioeconomic, medical and other information for the population of Sweden. Descriptions of these population and health registers along with register linkage studies are presented in detail below.

## 4.1 SWEDISH POPULATION AND HEALTH REGISTERS

### Total Population Register

The Total Population Register (TPR) contains annually collected data on the Swedish residents since 1968.[101] The TPR was used in this thesis to define the study population, and it also provided a range of sociodemographic characteristics for the study population, such as sex, year and month of birth, country and county of birth, date of death, date of immigration and date of emigration.

### Multi-Generation Register

The Multi-Generation Register (MGR) includes information on familial relations for the Swedish residents who were born in 1932 or later and registered in Sweden at any time since 1961.[102] In this thesis, the MGR was used to identify the study population in Studies I and IV. It was also used to extract information on reproduction-related factors (e.g., number of live births, age at childbirth), and to define familial relationship (i.e., identify maternal siblings).

### National Patient Register

The National Patient Register (NPR) contains data for public and private hospital discharges since 1964 (psychiatric diagnoses since 1973) and public and publicly funded specialized outpatient care since 2001.[103] The inpatient register has nearly complete nationwide coverage since 1987 (>99%), while the coverage for outpatient register is relative low (80%). The Swedish versions of the International Classification of Diseases Eighth (ICD-8, for the years 1968-1986), Ninth (ICD-9, for the years 1987–1996), and Tenth Revision (ICD-10, from 1997 onwards) codes were used to identify diagnoses recorded in the NPR.

### Medical Birth Register

The Medical Birth Register (MBR) provides information on prenatal, delivery, and neonatal period for around 98% of mothers and their newborn in Sweden since 1973. Data used in this thesis include maternal parity, age at childbirth, and smoking during pregnancy (available since 1982), as well as the newborn's multiple birth status, birth weight, and gestational age. In Study II, the MBR was also used to identify familial relationships for the study population including biological mother and maternal siblings.

### Archived obstetric records

Archived obstetric records were used to extract birth related information for our study population who were born before the start of the MBR. The records provide information on various maternal and newborn's characteristics.

**Longitudinal integrated database for health insurance and labor market studies**

The longitudinal integrated database for health insurance and labor market studies (LISA) contains annual data on registered adult Swedish residents (aged ≥16 years) since 1990 (since 2010, aged ≥15 years).[104] This thesis uses LISA to obtain information on education, occupation, and income.

**Census**

Censuses 1960-1990 were used in this thesis to provide information on study population's educational attainment, occupation, and income.

## 4.2 REGISTER LINKAGE STUDIES

This thesis uses data from three register linkage studies, that were created by merging relevant information from population-based registers described above. The linkage can be done by using the unique personal identification number that has been assigned to each Swedish resident on a permanent basis and remains unchanged throughout the lifetime.[105] The linkage of registers was however deidentified (i.e., without any personal identification numbers for the study participants).

### 4.2.1 Uppsala Birth Cohort Multigenerational Study

The Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen) is a representative and well-defined cohort of 14,192 males and females born in Uppsala University Hospital during the period of 1915-1929,[106] that has been combined with social and health data on all their descendants, obtained through Swedish routine registers.[107] This thesis is mainly based on the second generation female offspring who were born between 1933 and 1972. Considering that the majority of the study sample has social and health information recorded earlier than the start of the national registers, additional data was obtained from obstetric records and records from censuses. The UBCoS Multigen applies the life course approach to investigate early life determinants of heath and health inequalities in later life and across generations.

### 4.2.2 Swedish Interdisciplinary Panel

The Swedish Interdisciplinary Panel (SIP) is a longitudinal dataset comprised of several Swedish population and health registers. It contains detailed demographic, socioeconomic and health data for the total Swedish population born in 1973-1995, as well as their parents born outside the main sampling window.[108] This thesis uses SIP to explore the perinatal sociodemographic and health determinants of endometriosis among women born in Sweden in 1973-1987, also to assess the generalizability of our original findings from the UBCoS Multigen.

### 4.2.3 Psychiatry Sweden

'Psychiatry Sweden' (PS) is a population-based register linkage created by merging several national and local registers in Sweden. The database contains routinely collected longitudinal sociodemographic and health data on the entire Swedish population born in 1932-2011 and their descendants. The PS is designed for exploring research questions concerning the occurrence, predictors, and consequences of mental disorders.

## 4.3 ETHICAL CONSIDERATIONS

Studies I and IV are based on the UBCoS Multigen study. During the establishment of the study, information regarding utilizing and analyzing the data have been announced through newspapers. The UBCoS Multigen study was created as a linkage of register data without any personal identification numbers by the Statistics Sweden and data is stored at the Department of Public Health Sciences, Stockholm University. Analytical datasets only contain relevant variables for the respective study subjects. The study was approved by the Regional Ethics Committee in Stockholm, Sweden (dnrs: 03-117, 04-944T, 2009/1115-32, 2009/1830-32, 2014/2058-31/5, and 2016/715-32).

Studies II and III are based on two nationwide register linkage studies, namely the SIP and the PS. Requirement for informed consent was waived because these data sources were based on register data and study participants were deidentified. SIP was approved by the Regional Ethics Committee in Lund, Sweden (dnr: 2012/627). The data is stored and only accessible through Statistics Sweden's Microdata Online Access system. PS was approved by the Regional Ethics Committee in Stockholm, Sweden (dnrs: 2010/1185-31/5 and 2016/987-32). My analytical datasets only contain relevant variables to investigate the research questions and are stored in a KI server.

Epidemiological research in Sweden greatly benefits from availability of administrative (register) data and the unique personal identification number which enables comprehensive register-based data linkages. Although research databases are constructed as deidentified, potential ethical risks still exist. For example, epidemiological studies usually include various socioeconomic and health characteristics of the study participants, and the combination of these variables might result in potential identification of a specific person. The risk is particularly high for individuals who have extreme values on certain variables or suffered from a rare disease. It is therefore important that access to the data is strictly restricted to researchers who are in charge of the data analysis, and study findings are only reported at group level.

In addition, the goal of epidemiological studies is to benefit people who struggle with adverse health outcomes instead of stigmatizing any specific groups of people. For instances, the association between low birth weight and risk of endometriosis should not be treated as a reason to blame the mother. It is an integrated result of a wide range of socioeconomic, educational, cultural, and familial influences. Also, the comorbid condition between

endometriosis and several psychiatric disorders does not mean all woman with endometriosis necessarily suffered from mental illness, or vice versa.

One of the research aims of life course epidemiology is through exploring early life predictors/modifiable factors to identify high risk groups and therefore enable more effective preventive interventions. To this end, we have published our results in open science and carefully reported and interpreted our findings both in the research papers and when communicating in media. For example, the psychiatric comorbidity among women with endometriosis should be considered as a need to treat women with endometriosis from a multidisciplinary approach and a scientific evidence to promote timely diagnosis of both disorders. It is believed that a careful dissemination of study results to the public, patients, and health professionals benefit population health and outweigh the potential ethical risks.

## 4.4 MAIN MEASUREMENTS

Table 4.4 summarizes the register linkage, data sources, and main measurements used in each study. Descriptions of the main measurements are presented in detail below.

**Table 4.4** Summary of register linkage, data sources, and main measurements used in each study included in the thesis.

| Study | Register linkage | Data sources | Main measurements |
|---|---|---|---|
| I | UBCoS Multigen | Archived obstetric records | **Exposure:** birth weight, gestational age |
| | | MGR | Parental age at birth<br>Index women's number of live births, age at first and last birth |
| | | Census 1960 | Family socioeconomic position |
| | | Census 1960, 1970, 1990, LISA | Index women's adult education, income |
| | | NPR | Mother's endometriosis, index women's infertility<br>**Outcome**: Index women's endometriosis |
| II | SIP | LISA | **Exposure**: maternal education |
| | | MBR | Maternal parity, age at birth, smoking during pregnancy<br>Index women's birth weight, gestational age |
| | | TPR | Maternal country of origin, length of stay<br>Index women's birth county |
| | | NPR | Mother's endometriosis<br>**Outcome**: Index women's endometriosis |
| III | PS | NPR | **Exposure & Outcome**: endometriosis, psychiatric disorders |
| | | MBR | **Covariate**: Maternal age at birth<br>Index women's multiple birth status, birth weight |
| | | TPR | Birth county |

| | | | |
|---|---|---|---|
| | | LISA | Adult education |
| IV | UBCoS Multigen | Archived obstetric records | **Exposure**: birth weight, gestational age<br>**Covariate**: maternal age, marital status, parity |
| | | Census 1960, 1970, 1990, LISA | Parental education |
| | | NPR | **Outcome**: perimenopausal disorders |

### 4.4.1 Birth characteristics (all studies)

**Birth weight**

Birth weight in kilograms was classified into four categories, slightly different cut-points were used with consideration of sample distribution in each study. In Studies I and IV based on the UBCoS Multigen study, birth weight was classified as <3.0, 3.0-3.4, 3.5-3.9, ≥4.0 kg; in Studies II and III based on the total Swedish population, it was classified as <2.5, 2.5-3.4, 3.5-4.4, ≥4.5 kg.

**Gestational age**

Gestational age was measured as length of gestation in completed weeks. The estimation is based on either mother's self-reported first date of the last menstrual period or ultrasound examination. It was categorized as preterm birth (<37 weeks), full term (37-41 weeks), and post term (≥42 weeks).

**Birth weight-for-gestational age**

In Studies I and II, we focused on the effect of birth weight relative to gestational age, which is an indicator for fetal growth rate. It was created by standardizing birth weight by week of gestation, using the total Swedish female births as the reference (birth years 1973-1998 for Study I, 1973-1987 for Study II).

Other birth characteristics included in the thesis were birth county within Sweden (eastern, southern, northern Sweden), and multiple birth status (singleton, twins or more).

### 4.4.2 Parental characteristics (all studies)

Parental/maternal education was measured as the highest recorded educational level of either parent/the mother, and classified into elementary, secondary, shorter post-secondary, and university education. Family socioeconomic position (SEP) was based on the father's occupation, or the mother's occupation if the information was missing in the father. SEP was categorized as high, intermediate, and low. Other sociodemographic information including maternal and paternal age at childbirth (<20, 20-34, ≥35 years for the mothers, <25, 25-35, ≥36 years for the fathers), maternal marital status, and parity. Mother's region of birth was based on country of origin and classified according to countries similarities with respect to socio-cultural context. For the foreign-born mothers, length of stay in Sweden was calculated. Maternal smoking during pregnancy was prospectively recorded at mothers' first visit of antenatal care, usually during the first trimester.[109] This information is available for a

subgroup of index women who were born in 1982-1987 (Study II). Ascertainment for maternal endometriosis was same as for the index women which will be described in detail in section 4.4.4.

### 4.4.3 Adult characteristics (all studies)

Women's adult socioeconomic characteristics were highest achieved education and income. Reproduction-related factors including number of liveborn children, infertility history (diagnostic codes: ICD-7 636, ICD-8 628, ICD-9 628, and ICD-10 N97), as well as age at first and last childbirth.

### 4.4.4 Endometriosis (studies I, II, & III)

Endometriosis cases were identified as having a main or contributory diagnosis in the NPR during the respective follow-up period. Using the ICD, any endometriosis was defined as the ectopic presence of endometrial-type tissue at any site (ICD-8 code 625.3, ICD-9 code 617, and ICD-10 code N80).

In studies I and III, two endometriosis subtypes were further distinguished based on the presence of endometrial tissue outside or within the uterus, namely, external endometriosis (i.e., outside the uterus) using codes 625.30–625.32, 625.38, 625.39 (ICD-8), 617.B-617.X (ICD-9), N80.1-N80.9 (ICD-10); and uterine adenomyosis using codes 625.33 (ICD-8), 617.A (ICD-9), and N80.0 (ICD-10). In the analyses for subtypes, cases were identified as women having a first recorded respective subtype during the follow-up period (e.g., a woman does not get censored for external endometriosis if she has been diagnosed with adenomyosis previously).

A previous validation study has reported a positive predictive value of 97.8% for endometriosis cases recorded in the inpatient register, based on comparing with the respective patients' medical records.[103]

### 4.4.5 Psychiatric disorders (study III)

Study III aims to study the associations of endometriosis with a board spectrum of psychiatric disorders, nine groups of psychiatric disorders were considered. Cases were ascertained as having a diagnosis of the specific disorder in the NPR using the respective ICD codes listed in Table 4.4.5. Women were allowed to be classified as cases for more than one type of psychiatric disorder.

**Table 4.4.5** ICD codes for diagnoses of psychiatric disorders.

| Psychiatric disorders | ICD-9 | ICD-10 |
|---|---|---|
| Non-affective psychotic disorders | 295 (excluding 295H), 297, 298 (excl. 298B) | F20-24, F28, F29 |
| Bipolar and other affective psychotic disorders | 296, 295H, 298B | F25, F30, F31, F32.3, F33.3 |

| | | |
|---|---|---|
| Depressive disorders (excluding those with psychotic symptoms) | 300E, 311 | F32 (excl. F32.3), F33 (excl. F33.3), F34, F38, F39 |
| Anxiety and stress related disorders | 300A-D, 300F, 300G, 300H, 300W, 300X, 306, 307A, 308, 309 | F40-45, F48 |
| Eating disorders | 307B, 307F | F50 |
| Alcohol/drug dependence disorders | 291, 292, 303, 304 | F10-16, F18, F19 (all exclude 4th digit .0 and .9) |
| Personality disorders | 301 | F60-63, F68, F69 |
| Autism spectrum disorder | 299A, 299B, 299W | F84.0-F84.5 |
| Attention-deficit hyperactivity disorder | 314 | F90 |

### 4.4.6 Perimenopausal disorders (study IV)

Cases of perimenopausal disorders (PDs) were identified as the first recorded main or contributory diagnosis registered in the NPR at any time between 2001 and 2008. Using the ICD-10, PDs were classified into three subtypes: menopausal and climacteric states (code N95.1), perimenopausal bleeding (codes N92.4 and N95.0), and other PDs (codes N95.2, N95.8, and N95.9; e.g., atrophic vaginitis). We studied these subtypes of PDs separately in order to assess whether the potential developmental origins effect varies by the type of disorder. Therefore, women were allowed to be classified as cases for more than one subtype (e.g., a woman diagnosed with both perimenopausal bleeding and other PDs will be included both in the separate analyses for perimenopausal bleeding and other PDs). As such, incidence cases for each subtype were calculated from first recorded diagnosis for the specific disorder during the follow-up. It should be noted that to ensure these disorders are the results of natural menopause, women with a hysterectomy and oophorectomy were excluded or censored in the sensitivity analysis, defining these procedures through the Swedish Classification of Operations and Major Procedures (diagnostic codes: 7210, 7211, 7261, 7262, 7467, LCD00-04, LCC10, LCD10, LCD11, LEF13).[110] Also, women who diagnosed with artificial menopause (ICD-10 code N95.3) were not considered as cases.

# 5 STATISTICAL METHODS

## 5.1 SURVIVAL ANALYSIS

Survival analysis is a statistical technique to analyze time to event data. Since all the studies included in the thesis are based on longitudinal data and interested in time at diagnosis of a disease, survival analysis was used in all studies. In the analysis, individuals are followed from the time of origin, until an event of interest, events of censoring, or the end of the follow-up, whichever came first. Individuals may drop out from the study before experiencing the event of interest, due to emigration or death for instances; they could also stay event free at the end of the follow-up, these are right censored. Depending on the research question or time of origin, a timescale should be decided prior to the analysis, e.g., attainted age or time since diagnosis. In this thesis, age was chosen as the underlying timescale.

### 5.1.1 Survival analysis with time-dependent effect

The proportional hazards assumption is a strong assumption in Cox regression. It ensures the relative hazard is constant over follow-up time. There are several tests that can be utilized to assess the appropriateness of the proportional hazards. In this thesis, the assumption was tested through the Schoenfeld residuals method. If there is evidence of non-proportionality in the model, supplementary or alternative methods would be performed to model the interaction of an exposure with the underlying timescale.

In Study I, we detected that the proportional hazards assumption was violated for the association between our primary exposure (i.e., between birth weight-for-gestational age) and the outcome of interest (i.e., endometriosis). Thus, an alternative method, the flexible parametric survival model was applied to estimate the time-dependent effect of the exposure with regard to the underlying timescale (i.e., age at diagnosis of endometriosis).[111] In addition to estimate the regression coefficients as in the Cox model, the flexible parametric survival model estimates the baseline hazard (on the log hazard scale) and allows for interaction between the exposure and the underlying timescale.

In the flexible parametric survival model, the baseline hazard is plotted by the restricted cubic splines.[112] The splines consist of piecewise cubic polynomials joined through points called knots.[113] These knots together with some constraints (which restrict the fitted function to be linear outside the boundary knots) can ensure that the shape of the baseline hazard is smooth.[112] As such, the model could estimate the variations in hazard ratio over time. The number of knots is based on degree of freedom, which can be selected from an information criterion.[114] Since the hazard ratio is not constant over follow-up time, the flexible parametric survival model often presents the non-proportional (time-dependent) effect graphically.

### 5.1.2 Survival analysis with time-dependent exposure

Time-dependent exposure/covariate refers to when the status of an exposure/covariate changes over follow-up time, instead of being recorded before or at the start of the follow-up. It could be analyzed within the Cox proportional hazards regression model. Taking advantage of the prospectively collected longitudinal patient data, Study III explored the bi-directional temporal associations between endometriosis and psychiatric disorders. In this study, the exposure is the first diagnosis of the exposure disorder. The exposed time was calculated differently under three main scenarios: 1) if the woman was exposed before the start of the follow-up, the exposed time would be between the start and the end of the follow-up; 2) if the woman was exposed after the start of the follow-up, the exposed time would be between the time of first diagnosis of the exposure and the end of the follow-up, in other words, the woman would be treated as late entry at time of the exposure disorder; 3) if the woman was exposed after any censoring events (i.e., outcome occurs, death, emigration, or end of the follow-up), the exposed time would be considered as none.

## 5.2 ASSESSING UNMEASURED CONFOUNDING

Causation is a primary goal for epidemiological studies, as it will provide information on e.g., whether a disease can be prevented through modification of a certain exposure. Counterfactual-based approach to causal inference suggests that the causal effect of an exposure (or treatment) can only be estimated by comparing the potential outcomes from two hypothetical worlds: if everyone had been exposed and if everyone had not been exposed.[115] Since these two counterfactual scenarios can never be observed simultaneously in reality, an alternative is to assign individuals to be exposed and unexposed completely at random. In the absence of such ideal randomized experiments (commonly due to ethical and practical reasons), causal inference is usually made under conditional exchangeability in observational data through, among others, controlling for confounding. In an attempt to understand the causal nature of any observed associations, assessment for unmeasured confounding is one of the main issues to concern.

### 5.2.1 Family-based designs

One conventional way of controlling for confounding is through statistical modelling when measured early life factors that are the common causes of the exposure and the outcome are adjusted in the regression analysis. Nevertheless, the observed association could still be biased by unmeasured factors (e.g., genetic and other familial environmental factors) and thus spurious. As such, the observed association may be neither informative to causal interpretation nor relevant to public health prevention. To this end, family-based designs might provide an opportunity to address causality questions when randomized controlled trials are not practical.[29]

One commonly used family-based design is sibling comparison, where the effect of an exposure could be examined between individuals who were discordant for exposure status but raised in the same family and are genetically similar.[116] The result from a sibling comparison

model with adjustment for measured confounders would produce an informative estimate for the exposure-outcome association, in which measured confounders and unmeasured genetic or familial environmental factors shared by the siblings would be taken into account.

Study II applied a within-family comparison method to assess whether the observed associations at population level were confounded by residual confounding in analyses of exposures that vary between sisters. To do this, a "between-mother" variable was created to represent the average value of the exposure of interest within each family (clustered in mother); and a "within-mother" variable to represent the departure of each study subject from the family average value. These two variables were then fitted in the Cox regression model together with other measured confounders. To test residual confounding, Wald test was preformed to examine whether the estimated between-mother effect equals to the within-mother effect. If these two effects were statistically significantly different from each other, we interpreted these as evidence of residual familial confounding. This method was originally proposed and applied by Mann et al.[117]

Study III utilized a fixed-effect regression method with clustering on the families to account for residual familial confounding.[118] Specifically, the bi-directional associations between endometriosis and psychiatric disorders were estimated in the stratified Cox regression among families with at least two female children. By conditioning on family (clustered in mother), the model could automatically account for family-constant factors that were shared by the sisters, such as early childhood environment, parenting, or their genetic makeup. To further quantify the residual familial confounding, the effect of endometriosis on psychiatric disorders was tested by using the sister's endometriosis status among women without endometriosis. If the association was statistically significant, we interpreted such association as likely driven by shared familial liability.

### 5.2.2 E-value measure

E-value measure is a statistical tool commonly used in sensitivity analysis, which could assess how robust the observed associations are to unmeasured confounding. It can be used as a supplementary or alternative measure of family-based designs. This is because, first, family-based designs could still suffer from unmeasured non-shared confounding, and second, family-based designs require large sample size and detailed information on familial relations and, also, they may not be informative to explore the effect of family-constant exposures. Due to these reasons, E-value measure was used in Studies I and II to assess residual confounding. The E-value is defined as conditioning on measured confounders, how much unmeasured confounding would need to be associated with both the exposure and the outcome on the risk ratio scale that could fully explain away the observed effect or move the confidence interval to include null, but weaker confounding would not.[119] The method was originally proposed by VanderWeele and Ding.[119]

## 5.3 COUNTERFACTUAL-BASED MEDIATION ANALYSIS

Mediation analysis is commonly used in life course epidemiology, which could help identify mechanisms that explain the association between an early life exposure and an adult health outcome. Counterfactual-based mediation analysis is used in Studies I and II to decompose the total effect into direct effect (i.e., effect from the exposure independent from the examined mediators) and indirect effect (i.e., effect from the exposure explained through the examined mediators). The identification of counterfactual-based mediation effect is achieved under several assumptions, including no interference, consistency, and conditional exchangeability. One important assumption that needs to be carefully considered during study design and data analysis is the conditional exchangeability, which states that there should be no further confounding of the exposure-outcome, exposure-mediator, and mediator-outcome associations, conditional on measured confounders.[120]

In comparison to the traditional approach, the counterfactual approach to mediation analysis could accurately decompose the total effect into natural direct and indirect effects, as well as estimate the controlled direct effect in the presence of exposure-mediator interaction or intermediate confounding (i.e., confounder of the mediator-outcome association while affected by the exposure).[121,122] This thesis applied the g-computation procedure (gformula in Stata) to perform the counterfactual-based mediation analysis.[123] For causal conclusions, this method relies on all the aforementioned assumptions and inclusion of the exposure-mediator interaction in the presence of such statistically significant evidence.

# 6 STUDY SUMMARIES

## 6.1 STUDY I

### 6.1.1 Study population

Study I explored the associations of birth and early life characteristics with incidence of two subtypes of endometriosis. The study population was based on the second female generation of the UBCoS Multigen who were born between 1933 and 1972 with traceable birth records. Of 3476 women, we excluded 54 with multiple birth status, and 16 who had died or emigrated before the start of follow-up. The final analytical sample included 3406 women.

### 6.1.2 Design and statistical analysis

Cox regression was used with robust standard errors (SEs) to account for potential correlations between women born to the same mother. Women were followed from 15 years of age, or January 1, 1968, whichever came later. The follow-up continued until 50 years of age, or December 31, 2008, or death, emigration, or first diagnosis of the endometriosis subtype in question, whichever came earlier. All models were first adjusted for year of birth to account for potential period effect, and then earlier life confounding factors for the explanatory variable in question were additionally included in the model. Earlier life confounders were chosen separately for sets of explanatory variables that occurred at different life stages (i.e., birth, perinatal, and adult period). Birth weight-for-gestational age and gestational age were mutually adjusted in all models, to distinguish the effects of being born earlier versus slow fetal growth trajectory. Considering the small number of cases for adenomyosis, it was modelled only with the adjustment for birth year.

Mediation analysis was conducted to examine the role of index women's adult characteristic (i.e., number of live birth) with respect to the total association between birth weight-for-gestational age and endometriosis.

Since the proportional hazards assumption was violated for the association between between birth weight-for-gestational age and endometriosis, it was further examined through the flexible parametric survival model to estimate and plot the time-dependent effect of between birth weight-for-gestational age on endometriosis over follow-up time. The E-value measure was used to assess the robustness of the total association with respect to unmeasured confounding.

### 6.1.3 Results

In the analytical sample, 111 (3.3%) women have received an endometriosis diagnosis, corresponding to an incidence rate (IR) of 1.08 per 1000 woman-years. There were two peaks in the incidence of any endometriosis, the early peak was around age 25 and predominantly contributed by external endometriosis cases. The later peak was around age 45 consisted by both external endometriosis and uterine adenomyosis cases (Figure 6.1.3.A).

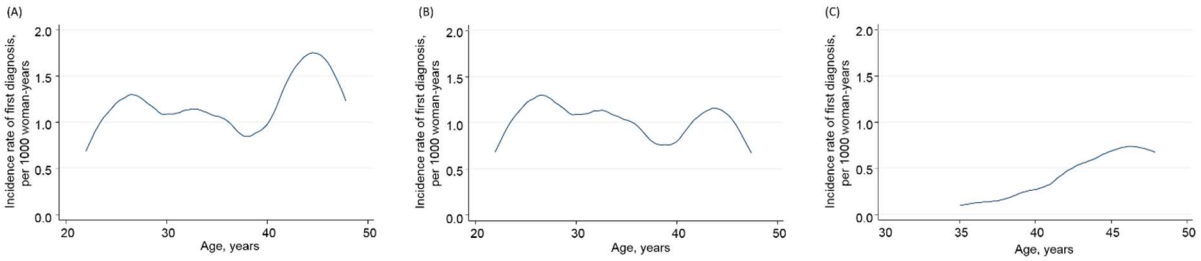


**Figure 6.1.3.A** Incidence rate of first diagnosis with (A) any endometriosis (n=111), (B) external endometriosis (n=91), and (C) uterine adenomyosis (n=24). **Note**: Figure 1 in Study I.

### Associations with birth and perinatal characteristics

Figure 6.1.3.B shows the time-dependent effect of birth weight-for-gestational age on any endometriosis. On average, lower birth weight-for-gestational age was associated with increased incidence of any endometriosis. The association was attenuated when endometriosis was diagnosed at later reproductive life, the stage when half of the cases were adenomyosis. This points to the same direction as findings of the two subtypes. Specifically, birth weight-for-gestational age showed a proportional and inverse association with external endometriosis (adjusted hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.13-1.84, per SD decrease), but not with adenomyosis. Gestational age, on the other hand, was not associated with any type of endometriosis (Figure 6.1.3.C). The E-value measure indicated that the association between birth weight-for-gestational age and endometriosis was rather robust to unmeasured confounding.

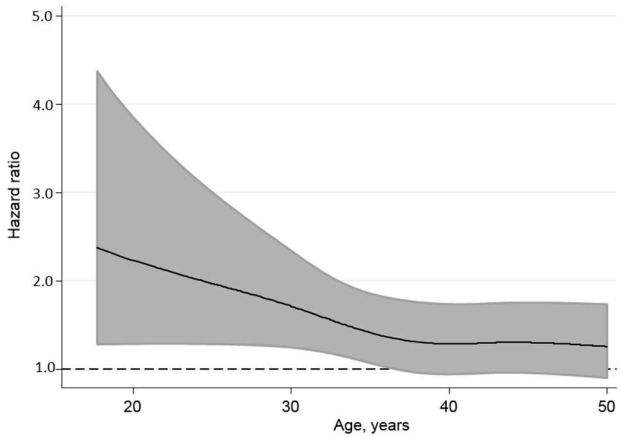


**Figure 6.1.3.B** Time-dependent association between birth weight-for-gestational age and any endometriosis. **Note**: the black curve shows the ratios between 25$^{th}$ and 75$^{th}$ percentiles of birth weight-for-gestational age with adjustment for birth year and gestational age. Grey area shows the 95% CI. Figure 2 in Study I.

There was no evidence for associations of family socioeconomic position and maternal age with any type of endometriosis. Older paternal age was associated with a lower incidence of external endometriosis in the daughter, but not with adenomyosis. Maternal endometriosis

history was a strong predictor for daughter's external endometriosis. Adjustment for other perinatal factors makes little change to these associations (Figure 6.1.3.C).

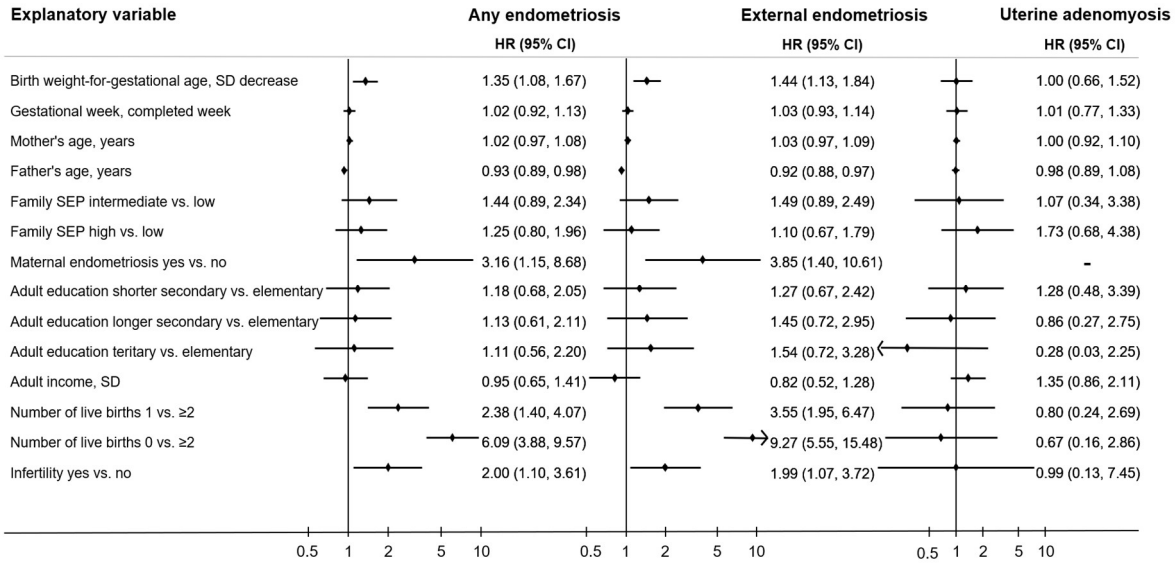


**Figure 6.1.3.C** Associations of birth, perinatal and adult characteristics with rate of endometriosis and its two subtypes (n=3406). **Note**: SD, standard deviation; SEP, socioeconomic position. Estimates for any and external endometriosis adjust for birth year and (other) perinatal characteristics; estimates for adenomyosis adjust for birth year; plus birth weight-for-gestational age and gestational age were mutually adjusted in all analyses. This figure was based on estimates from Table 2 in Study I.

### Associations with adult characteristics

Neither index women's adult education nor income was associated with endometriosis. Number of live births showed an inverse dose-response association with external endometriosis but presented a non-significant opposite trend with adenomyosis. However, mediation analysis showed that number of live births could only explain a limited proportion of the inverse association of birth weight-for-gestational age with any and external endometriosis (4% and 2%, respectively). Women with prior infertility disorder were at 2-fold increased rate of external endometriosis, but not adenomyosis (Figure 6.1.3.C).

## 6.2 STUDY II

### 6.2.1 Study population

Study II investigated the associations of perinatal characteristics with endometriosis in a nationwide cohort of women born in Sweden between 1973 and 1987. Starting from 688 412 singleton women, we excluded 0.8% who died, and 3.4% who emigrated before their fifteenth birthdays. A further 5.3% were excluded due to missing information on explanatory variables, and a 0.007% were excluded due to implausible combinations of birth weight and length of gestation. The final analytical sample included 628 312 singleton women.

### 6.2.2 Design and statistical analysis

Cox regression with robust SEs was utilized to follow women from their 15 years of age, continue until December 31, 2012, or death, emigration, or first diagnosis of endometriosis, whichever came earlier. All explanatory variables were first modelled with endometriosis with the adjustment for year of birth, measured maternal characteristics were additionally adjusted in the final model.

Within-family comparison was applied to examine whether the observed associations were likely the result of unmeasured familial confounding, it was used for the explanatory variables that are commonly differed between sisters. For the same aim, E-value was used for the explanatory variables that are constant within families. These methods were described in detail in sections 5.2.1 and 5.2.2. The potential mediation effect of birthweight-for-gestational age in the associations between maternal characteristics and endometriosis was also assessed.

### 6.2.3 Results

Among women aged 15-40 years, 8262 (1.3%) received an endometriosis diagnosis during the observation period, corresponding to an age-specific IR of 0.77 per 1000 woman-years.

**Associations with maternal characteristics**

Figure 6.2.3.A shows the associations of maternal characteristics with endometriosis. Higher maternal educational level showed a dose-response association with endometriosis, specifically, the rate was 16% (95% CI, 9%-22%) lower for women with mothers of university degree compared to those born to mothers with elementary education. We found a higher incidence of endometriosis among women born to mothers who came from other Nordic countries and the former Soviet states, but these associations could not be explained by mother's length of stay in Sweden (data not shown).

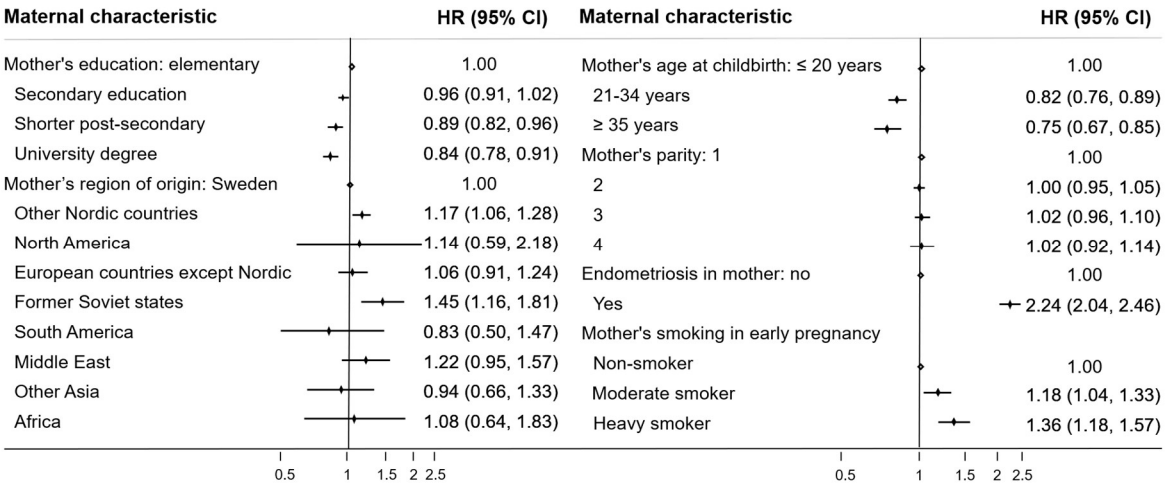


**Figure 6.2.3.A** Associations of maternal characteristics with rate of endometriosis among women born in Sweden in 1973-1987. **Note**: Estimates adjust for birth year and other maternal characteristics except for mother's smoking. Estimates for mother's smoking were based on a

subgroup of women born in 1982-1987 (n=203 891) and adjust for other maternal characteristics. This figure was based on estimates from Table 2 in Study II.

As shown in the right part of Figure 6.2.3.A, higher maternal age was associated with decreased incidence of endometriosis in daughters. This association was however attenuated to non-significant in the within-mother analysis, suggesting that unmeasured familial confounding may account for the association rather than a true causal effect (data not shown). Mother's parity was not related to daughter's endometriosis. Expectedly, mother's endometriosis history was a strong predictor for the increased incidence of endometriosis in daughters. We found maternal smoking during pregnancy predicted a higher incidence of early onset of endometriosis in daughters, independent from other measured maternal characteristics and unmeasured familial factors shared by the sisters.

**Associations with birth characteristics**

Both the absolute and relative measures of birth weight showed independent inverse associations with endometriosis. Within-family analysis for birth weight-for-gestational age further indicated no evidence of residual familial confounding. Mediation analyses showed that birth weight-for-gestational age could explain 26% of the total association between maternal smoking and endometriosis. Whereas length of gestation was not associated with endometriosis. Women born in southern Sweden had slightly increased incidence of endometriosis compared to those from the eastern part. (Figure 6.2.3.B)

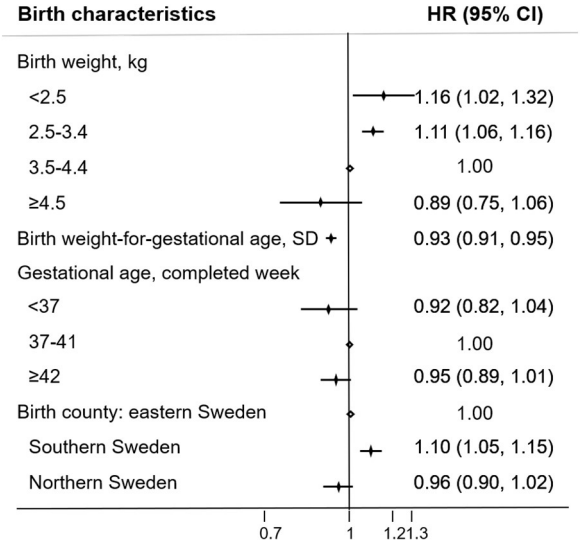


**Figure 6.2.3.B** Associations of birth characteristics with rate of endometriosis among women born in Sweden in 1973-1987. **Note**: Estimates adjust for birth year and maternal characteristics except for mother's smoking. This figure was based on estimates from Table 2 in Study II.

## 6.3 STUDY III

### 6.3.1 Study population

Study III explored the bi-directional associations between endometriosis and psychiatric disorders in a nationwide cohort of all live female births in Sweden between 1973 and 1990. Of 893 716 women, we excluded 7555 who died, 31 798 who emigrated, and 2 who received an endometriosis diagnosis before their fourteenth birthdays, giving an analytical sample of 854 361 women. Sibling comparison analysis was conducted in a subsample of 173 650 families, which contained at least two female births born from the same mother during the study period.

### 6.3.2 Design and statistical analysis

Cox regression with time-dependent exposure modelling was used to account for women who received a diagnosis of the exposure disorder before or during the follow-up. Women were followed from 14 years of age until December 31, 2016, or death, emigration, or first diagnosis of the outcome disorder in question, whichever came earlier.

All bi-directional associations were adjusted for women's year of birth, then measured birth characteristics along with women's educational level were included in the fully adjusted model. The main analyses were repeated in a fixed-effect model with clustering on the families with at least two female children by using the stratified Cox regression with the adjustment for measured confounders. By design, the model is expected to additionally adjust for unmeasured familial factors shared by the sisters. To further quantify unmeasured familial confounding, logistic regression was used to compare the odds of psychiatric disorders using sister's endometriosis status in a subsample of women without endometriosis. These associations were adjusted for birth year and measured confounders.

For sensitivity analyses, first, our main analyses were repeated separately for two endometriosis subtypes to explore whether the observed associations vary by type of endometriosis. Second, to partially account for the potential diagnostic delay in both endometriosis and psychiatric disorders, we repeated the main analyses by including a six-month lag time in between the exposure and the outcome disorders.

### 6.3.3 Results

In a nationwide cohort of women aged 14-43 years during the observation period of 1987-2016, 14 144 (1.7%; IR, 0.84 per 1000 woman-years) of them received an endometriosis diagnosis. In this cohort, anxiety and stress-related disorders and depressive disorders were the two most prevalent psychiatric disorders, which affect 111 847 (13.1%; IR, 6.91 per 1000 woman-years) and 79 232 (9.3%; IR, 4.82 per 1000 woman-years) women respectively. The age-specific IRs for these two common psychiatric disorders and endometriosis reached peak around age 30, whereas most other psychiatric disorders peaked at earlier ages.

**Endometriosis and later diagnosis of psychiatric disorders**

At population level (first column of HRs in Figure 6.3.3.A), after adjustment for birth year, birth characteristics, and educational level, women with endometriosis showed increased rates of being later diagnosed with all groups of psychiatric disorders, with the exception for autism spectrum disorder (ASD). The HRs ranged from 1.93 (95% CI, 1.71-2.18) for alcohol/drug dependence disorders to 1.30 (95% CI, 1.00-1.69) for non-affective psychotic disorders. In the sibling comparison analyses (second column of HRs in Figure 6.3.3.A), compared to unaffected sisters, women with a previous endometriosis remained at higher risk of being diagnosed with depressive disorders, anxiety and stress-related disorders, alcohol/drug dependence disorders, and attention-deficit hyperactivity disorder (ADHD), with the highest HR observed for ADHD (HR, 1.98; 95% CI, 1.34-2.93).

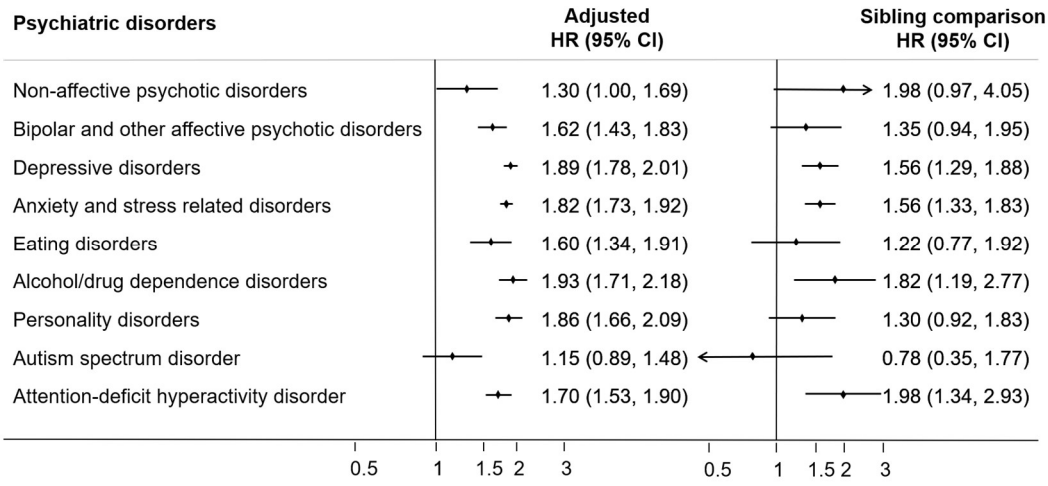


**Figure 6.3.3.A** Hazard ratios for diagnosed psychiatric disorders following a diagnosis of endometriosis. **Note**: adjusted HRs were adjusted for birth year, birth characteristics and education; same set of factors were adjusted in sibling comparison HRs along with unmeasured familial factors shared by the sisters. This figure was based on estimates from Table 2 in Study III.

### Psychiatric disorders and later diagnosis of endometriosis

The fully adjusted population-level analyses showed that all examined psychiatric disorders except for non-affective psychotic disorders were associated with an increased rate of being later diagnosed with endometriosis (first column of HRs in Figure 6.3.3.B). The associations with alcohol/drug dependence disorders and ASD were attenuated to non-significant when unmeasured familial factors were considered through comparing sisters exposed and unexposed to the respective psychiatric disorder (second column of HRs in Figure 6.3.3.B).

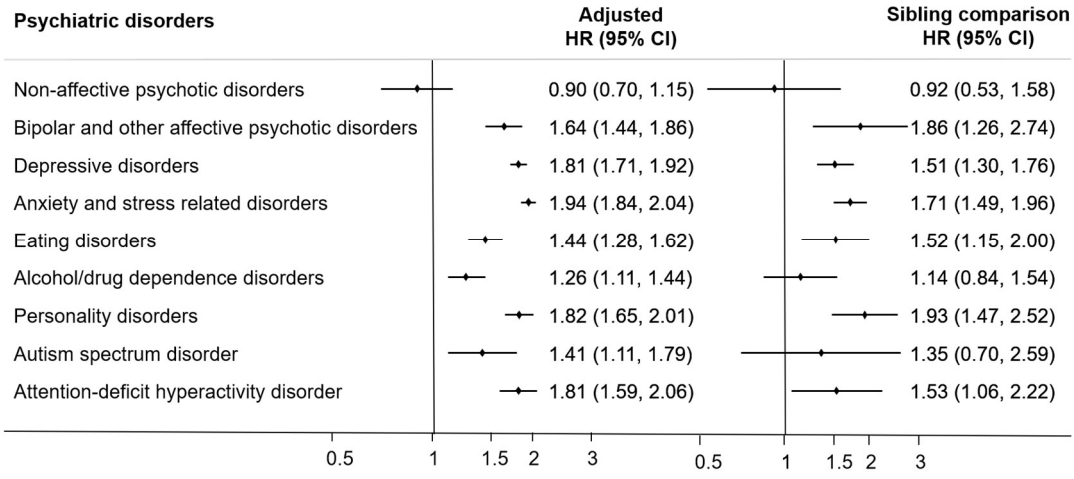


**Figure 6.3.3.B** Hazard ratios for diagnosed endometriosis following a diagnosis of psychiatric disorder. **Note**: adjusted HRs were adjusted for birth year, birth characteristics and education; same set of factors were adjusted in sibling comparison HRs along with unmeasured familial factors shared by the sisters. This figure was based on estimates from Table 3 in Study III.

In sensitivity analyses restricting to women without a diagnosed endometriosis, having a sister with endometriosis was associated with increased odds of being diagnosed with

depressive disorders, anxiety and stress related-disorders, personality disorders, and ADHD. The analyses of including a six-month lag time in between the exposure and the outcome disorders only slightly attenuated the bi-directional associations both in the population-based and sibling comparison models (data not shown).

## 6.4 STUDY IV

### 6.4.1 Study population

Study IV explored the associations of birth characteristics with three subtypes of perimenopausal disorders (PDs). The study population was based on the second female generation of the UBCoS Multigen, who were born between 1936 and 1968. Of a total of 4290 singleton women, we excluded 258 who died or emigrated before the start of follow-up, and 820 whose birth records were not available This resulted in a final analytical sample of 3212 women. There was no statistically significant difference in the incidence of any subtypes of PDs between women with available birth records and those without (all P>0.10).

### 6.4.2 Design and statistical analysis

Cox regression with robust SEs was used to estimate the main associations. Follow-up started from when women turned 40 years of age, or January 1, 2001, whichever was latest, and continued until when they turned 65 years of age, or December 31, 2008, or death, emigration, or first diagnosis of the disorder in question, whichever was earliest. The main exposures, birth weight and gestational age were modelled as continuous variables, as there was no evidence of nonlinearity, when including a quadratic term in the model (all P>0.26). Analyses were first adjusted for birth year, and birth weight was additionally adjusted for gestational age. Then parental characteristics were further included in the model. In sensitivity analysis, to assess the robustness of our study findings with regard to natural menopause, we excluded women who had a hysterectomy or oophorectomy from the study sample and censored women at these events during the follow-up. All statistical analyses in this thesis were performed in Stata versions 14 and 15 (StataCorp).

### 6.4.3 Results

In the analytical sample, 218 women (6.8%) received a PD diagnosis, which included 125 women diagnosed with menopausal and climacteric states, 61 women with perimenopausal bleeding, and 58 women with other PDs (e.g., atrophic vaginitis or other unspecific PDs). Incidence of menopausal and climacteric states increased gradually from age 45 to 65, while other PDs showed up later from age 50. In contrast, perimenopausal bleeding was predominantly diagnosed before age 55 (Figure 6.4.3).

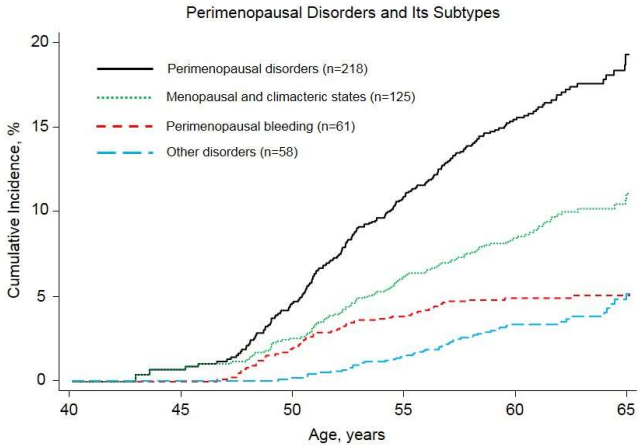


**Figure 6.4.3** Cumulative incidence of first diagnosis with any perimenopausal disorders and its three subtypes. **Note**: Figure 1 in Study IV.

Women diagnosed with menopausal and climacteric states were more likely to be highly educated or born to well-educated parents. Higher maternal parity was related to higher incidence of being diagnosed with other PDs. Perimenopausal bleeding disorder was more commonly diagnosed among women with more children.

After adjustment for birth year and gestational age, birth weight was positively associated with incidence of menopausal and climacteric states. Specifically, the rate was 66% (95% CI, 14%-141%) higher per kilogram increase in birth weight. Length of gestation was not associated with incidence of menopausal and climacteric states (Table 6.4.3).

Neither birth weight nor gestational age showed statistically significant association with perimenopausal bleeding disorders. Birth weight was not associated with other PDs. Instead, rate of other PDs was lower among women born at older gestational age (minimally adjusted HR, 0.87; 95% CI, 0.79-0.95). Additional adjustment for parental characteristics did not change these results significantly (Table 6.4.3). These findings remained largely similar in the sensitivity analysis with censoring for hysterectomy and oophorectomy (data not shown).

**Table 6.4.3** Associations of birth characteristics with rate of three subtypes of PDs (n=3212).

| **Birth characteristics** | **Menopausal and climacteric states** | | **Perimenopausal bleeding** | | **Other PDs** | |
|---|---|---|---|---|---|---|
| | **HR (95% CI)** | | | | | |
| | Minimally adjusted[a] | Further adjusted[b] | Minimally adjusted[a] | Further adjusted[b] | Minimally adjusted[a] | Further adjusted[b] |
| **Birth weight, kg** | 1.66 (1.14-2.41) | 1.59 (1.09-2.33) | 0.73 (0.42-1.27) | 0.74 (0.42-1.33) | 1.29 (0.79-2.10) | 1.09 (0.65-1.83) |
| **Gestational age, completed week** | 1.00 (0.91-1.10) | 1.00 (0.91-1.10) | 0.90 (0.80-1.01) | 0.90 (0.81-1.00) | 0.87 (0.79-0.95) | 0.86 (0.78-0.94) |

CI, confidence interval; HR, hazard ratio; PD, perimenopausal disorder.
[a] Minimally adjusted models adjust for birth year; birth weight was additionally adjusted for gestational age.
[b] Further adjusted models additionally adjust for parental education, mother's marital status, age, and parity at birth.
Adapted from Table 2 in Study IV.

# 7 DISCUSSION

## 7.1 INTERPRETATION AND IMPLICATIONS

### 7.1.1 Developmental origins of endometriosis

In Study I and II, we have investigated the developmental origins effect with respect to endometriosis, a common chronic condition affecting women of reproductive age. In study I, we were able to follow women's entire reproductive period and showed that lower birth weight relative to gestational age was associated with risk of endometriosis, particularly when onset of the disorder occurred during the early to the mid-reproductive period (i.e., between ages 15-40 years). This association was further confirmed in Study II by analyzing a nationwide cohort of females, although women were relatively younger at the end of follow-up period (i.e., aged 25-40 years) compared to Study I.

Our results are consistent with previous studies regarding the inverse association between birth weight and endometriosis, and also extend those findings by showing that the effect from low birth weight was mainly driven by the slow fetal growth rate rather than being born prematurely.[18,20,124] Slow fetal growth is a marker for a range of adverse conditions during the earliest stage of development, such as fetal malnutrition, alterations in endocrine status, less functional capacity of the reproductive organs.[17,125] As human beings are sensitive and capable of adapting to the environment,[14] these harsh early conditions may cause a series of responses in the body, such as alterations in hormone secretion or tissue hormone sensitivity.[17] All of these could contribute to the development of endometriosis, an estrogen-dependent disease regulated by ovarian steroid production.

In addition, low birth weight has been linked with impaired function of immune system in later life,[126] this is crucial as the immune-system dysregulation is one of the sufficient causes for endometriosis.[60]

Moreover, our studies suggest that the inverse association between birth weight-for-gestational age and endometriosis was rather robust to familial confounding. This is supported by the association remaining the same in both cases: on adjustment for maternal endometriosis (in Study I), and in within-family comparisons by controlling for unmeasured genetic and familial environmental factors shared by the siblings (in Study II).

### 7.1.2 Maternal smoking and risk of endometriosis

To our best of knowledge, this research is the first prospective study based on the total-population to investigate the effect of in utero exposure to smoking on endometriosis. A clear positive dose-response association was found between maternal smoking during pregnancy and daughters' endometriosis risk during early to mid-reproductive period. The association was also confirmed in the within-family analysis, indicating shared familial confounding was unlikely to fully explain the increased risk.

Previous findings on the effect of in utero exposure to smoking were conflicting and inconclusive, with interpretations limited by the fact that they were based on retrospectively collected data on exposure status and relatively low statistical power (range, 32-310 cases).[24,127-129]

Evidence on the effect of adult smoking was rather consistent and suggested a protective effect on endometriosis, potential mechanism involve reduced estrogen levels caused by smoking.[71,130] It is unfortunate that we could not study the effect of adult smoking and its role with regard to the association between intrauterine exposure to smoking and endometriosis.

We however speculate that the mechanism for exposure to smoking in utero is different compared to adult direct smoking. It could be that in utero exposure to dioxins or other toxic components caused by mother's smoking decreased the functional capacity of immune system in the fetuses and thereby made them susceptible to inflammation and ectopic endometrium.[131] This speculation is supported by studies on both animals and humans, in which environmental exposure to dioxin has been found to increase the risk of endometriosis due to impaired immune defense.[65,66] In light of this, elevated risk of endometriosis has also been found among women who were exposed to passive smoking during childhood.[132]

### 7.1.3 Other parental and adult characteristics with risk of endometriosis

In this thesis, we also explored whether exposures across life may exert life course or intergenerational effects on endometriosis. Specifically, we looked at other maternal or paternal health, socioeconomic and demographic characteristics as well as women's own adult characteristics and subsequent risk of endometriosis.

As expected, we found that mother's endometriosis history was strongly associated with the risk of endometriosis in daughters. This evidence reflects the heritable nature of endometriosis, in line with many previous studies.[63,133,134] In studies I and II, we have identified inverse associations of paternal age and maternal age at birth with daughter's endometriosis at population level. The association with maternal age, however, was found to be spurious in the within family comparison through accounting for unmeasured familial confounding. The protective effect of higher father's age on daughter's endometriosis is intriguing but may also suffer from familial confounding. Unfortunately, this thesis was unable to further investigate the potential confounding bias and underlying mechanism due to unavailability of data, but we will strive to revisit this finding in the future.

We did not detect any significant associations between index women's highest education and adult income with endometriosis. The lack of association with education has also been shown in a Norwegian study,[69] however, it is inconsistent with findings from North America where excess risk was found among women with higher socioeconomic positions.[67,68] We speculate that this inconsistency could partially be driven by variation in the ability to access to healthcare in different social contexts. In the U.S., for example, poor access to healthcare may lead a considerable proportion of undiagnosed cases among women from lower socioeconomic positions, which would artificially lower their observed incidence rate. In

contrast, the egalitarian healthcare system in Nordic countries ensures women have relatively equal access to medical care regardless of their socioeconomic conditions. We additionally noticed that the incidence of endometriosis was higher among women born to mothers with lower educational level.

Moreover, we found elevated risk of endometriosis among women who were born to mothers who came from other Nordic countries and from the former Soviet states. The higher risk of endometriosis for women with mothers originally from other Nordic countries compared to Swedish-born mothers is indirectly in agreement with a previous Swedish study based on women's own country of origin.[72] Evidence for a higher risk of endometriosis among women born to mothers from the former Soviet states is limited. We speculate that this association might be partially related to perceived psychosocial stress among women during their childhood, which is a contributing factor to endometriosis.[135] This potential mechanism however deserves more research.

For adult reproductive characteristics, we found lower number of live births and prior infertility disorder to predict subsequent risk of external endometriosis. The risk was however not related to women's ages at first and last birth. The inverse dose-response association between number of live births and later risk of endometriosis is expected and well in line with the menstrual reflux mechanism. Menstrual reflux is one of important prerequisites for the development and establishment of endometriosis, therefore more frequent exposure to menstruation among women with fewer children will increase the chance for endometrial fragments to implant in the peritoneal cavity and result in ectopic uterine mucosa.[62] In addition, the high levels of progestin and prolactin during pregnancy and lactation might inhibit the progress of endometriosis through interrupting regular estrogen production.[131] Nevertheless, considering infertility is a known consequence of endometriosis, and we can only capture the time at diagnosis instead of onset of the disorder, fewer live births might thus be a result rather than the cause for endometriosis.

The menstrual reflux mechanism however does not apply to uterine adenomyosis. We detected a non-significant trend towards a higher risk of adenomyosis among women with greater number of live births. The potential underlying mechanism might be their more frequent exposure to uterine trauma, which has been suggested as a pathogenesis of adenomyosis.[76 77]

### 7.1.4 Psychiatric comorbidity in women with endometriosis

It is well known that endometriosis could lead to psychological suffering,[25,26] due to its incurable condition and related consequences, such as chronic pelvic pain, dysmenorrhea, and infertility. However, considering that endometriosis and mental disorders are both mainly heritable, the psychiatric burden among women with endometriosis may be caused by underlying familial confounding. In Study III, we identified a broad comorbidity between endometriosis and many psychiatric disorders. Our findings also showed that shared familial liability could only partially explain these comorbid associations. Therefore, apart from

familial susceptibility to both disorders, other explanations may account for the overlap between endometriosis and many mental disorders.

We speculate that common causes including immune dysregulation and early exposure to environmental contaminants, such as polychlorinated biphenyls and dioxins may contribute to the progression of endometriosis and multiple mental disorders, making women susceptible to develop both conditions.[9,65,136-138] The higher rates of being later diagnosed with mental disorders in women with prior endometriosis could be the direct result of adverse consequences of endometriosis, which may amplify mental distress in these women.[80,139-141] The medical care for physical consequences of endometriosis, e.g., pelvic pain, could also increase the detection or diagnosis of mental disorders among affected women. Additionally, some common hormonal medications used to treat the symptoms or consequences of endometriosis, e.g., gonadotropin-releasing hormone agonists and oral contraceptives have been linked to multiple psychiatric side effects and could potentially increase the risks of depression and anxiety disorders among the users.[142-147]

We also found that there was an increased risk of being later diagnosed with endometriosis among women with mental disorders. This could be explained by increased detection given that women with mental ill health may be already in contact with healthcare. It could also be that women with psychiatric disorders may suffer from more severe endometriosis symptoms thus more likely to be diagnosed.[148,149]

Despite the fact that the bi-directional associations observed in our study might be biased by reverse causality, our findings nevertheless demonstrated a high degree of comorbidity between endometriosis and many mental disorders. Clinically, the psychiatric comorbidity in women with endometriosis should be better recognized and treated with a multidisciplinary approach.

### 7.1.5 Developmental origins of perimenopausal disorders

From study I and II, we found out that there is a developmental origins effect on a common female hormone-related disorder during the reproductive years, namely endometriosis. In study IV we have investigated whether a similar effect could be identified for perimenopausal disorders (PDs), a group of disorders also partially driven by hormonal changes in the end/after the reproductive period. Contrary to the negative effect from low birth weight on endometriosis, we found that high birth weight was associated with an increased risk of menopausal and climacteric states, such as hot flushes, sleeplessness, and headache.

Unlike other important female health burdens, e.g., reproductive cancers and early menopause,[150-152] evidence on the developmental origins effect with regard to PDs was limited. It was thus difficult for us to compare our results with previous research directly. But we speculate that one possible explanation for the observed positive association between birth weight and risk of menopausal and climacteric states is through adult overweight or obesity caused by higher birth weight.

It is well-known that higher weight at birth is associated with higher body mass index (BMI) or obesity in adulthood.[153] The association between adult BMI and menopausal symptoms is nevertheless not straightforward. An earlier large population-based cohort study showed that higher adult BMI was associated with less risk of experiencing menopausal symptoms among postmenopausal women.[154] A possible explanation is that menopausal symptoms, particularly vasomotor-related symptoms, are improved by high estrogen levels produced by the greater quantities of adipose tissue during postmenopausal period.[155,156]

However, inverse associations of adult BMI with estrogen levels and menopausal symptoms were found among perimenopausal women or women who undergo menopausal transition.[100,157-159] For example, a previous study based on perimenopausal women (45-54 years) showed that higher BMI was associated with an increased risk of hot flushes. Potential mechanisms involve lower estradiol levels and earlier onset of ovarian insufficiency (one phenomenon of early menopause) in obese women.[99] Relatedly, previous studies have suggested an association between higher birth weight and earlier menopause, although the role of adult BMI mediating such association was not investigated.[27,28]

Taken together, we speculate that the observed positive association between birth weight and menopausal and climacteric status in our study could be indirectly explained by higher adult BMI and lower estrogen levels during perimenopausal period. This speculation is partly supported by many studies in which adult BMI was found negatively associated with estradiol in women during premenopausal period but reversed during postmenopausal period.[160-162] Nevertheless, further research is warranted into the underlying mechanism, including potential upstream determinants such as maternal diabetes or overnutrition during the fetal period.

In this study we also found that the risk of perimenopausal bleeding disorders was not related to birth weight or gestational age. This lack of association is somewhat expected, considering perimenopausal abnormal bleeding is an indicator of potential gynecological lesions or malignancies, which were found not to be related to birth weight according to a meta-analysis.[150]

We speculate that the association between shorter length of gestation and other PDs, e.g., vaginal or endometrial atrophy could reflect the influence from the prenatal period on the development of ovarian function and reproductive organs. To sum up, Study IV supports the developmental origins theory with respect to PDs and suggests that the prenatal period is a sensitive period for organ development and subsequent disease risk in which non-optimal intrauterine environment may have long-term effects on health even during the perimenopausal period.

## 7.2 METHODOLOGICAL CONSIDERATIONS

### 7.2.1 Misclassification and generalizability

The use of longitudinal data prospectively collected from comprehensive population-based registers is the main strength of this thesis. However, our register-based design to identify cases is also a source of limitation towards potential misclassification, and this applies to all health outcomes examined in this thesis, i.e., endometriosis, psychiatric disorders, and PDs.

We used secondary care data from hospitalization and outpatient specialist records to ascertain cases, thus women with a disorder in question who did not seek medical care would not be captured and will be treated as disorder-free. Presumably, we might miss a considerable number of cases among women who did not seek medical care due to less severe symptoms, not being accurately diagnosed, or treated within primary care. The potential under-diagnosis of cases could also explain why prevalence of endometriosis or PDs found in this thesis was lower than when estimated from population level or survey-based design.[54,92] Nevertheless, we think the outcome misclassification is unlikely to be differential with regards to exposure status, for example, a woman would not be overlooked for endometriosis because of her lower weight at birth, which would not bias our observed associations.

Misclassification bias might be more pronounced in sibling comparison analysis in Study III, considering that both endometriosis and psychiatric disorders tend to cluster within families, e.g., women with endometriosis might imply an undiagnosed condition in the "unexposed" sister. If some pairs of sisters who are in reality concordant for the exposure were treated as discordant in the sibling analysis, then the true association will be underestimated. It is however possible that this misclassification bias could be somewhat counterbalanced by the potential carryover effect among sisters, e.g., endometriosis condition in one sister might increase the detection in another sister.

Moreover, the potential misclassification limits the generalizability of our study findings to women with subclinical symptoms of mental disorders and those with milder symptoms of endometriosis and PDs.

### 7.2.2 Confounding

In this thesis, we have tried to reduce confounding bias through adjustment for prospectively recorded earlier life factors than the exposure, the E-value measure, and family-based designs. However, in both conventional confounding controlled model and family-based designs, study findings may still be biased from unmeasured factors that are causally linked with both the exposure and the outcome but are not on the causal pathway. If this is the case, any observed associations from sibling comparison analysis will be more biased by non-shared confounding than population level analysis.[163]

### 7.2.3 Sibling comparison

Apart from inability to control unmeasured family-varying confounding factors, the sibling comparison may also be biased by "accidently" controlling for shared covariates that are on the causal pathway of the exposure-outcome association. The adjustment for potential mediators shared by the sisters may dilute the true causal effect from the exposure.[164] Therefore, if attenuation in estimations was observed in sibling comparison analysis compared to population-level analysis, the results should be interpreted with caution. The lack of relationships in some exposure-outcome associations in Studies II and III may not only be explained by the presence of shared confounding (e.g., genetic or familial environmental factors) but may also be due to shared mediators (e.g., living conditions, physical health, or life-style factors) or simply result from low statistical power in the reduced sample size.

In addition, the sibling comparison design assumes no sibling carryover or contagion effects, which means the exposure and outcome of one sibling should not affect the exposure and outcome of the other sibling(s).[165] In Study II, considering the long-term associations of maternal and birth characteristics with endometriosis in reproductive period, estimations from within-family analysis are unlikely to be affected by carryover effect. Although it is possible that maternal smoking in the previous pregnancy may increase the risk of the same behavior in the current pregnancy, the results would be less biased in the presence of this type of exposure-to-exposure carryover.[165]

The associations of endometriosis with psychiatric disorders in Study III may however be biased by the outcome-to-outcome carryover (contagion) effect, e.g., psychiatric disorder in one sister may affect the mental health in another sister. In this case, we may underestimate the true association between endometriosis and psychiatric disorders.

## 7.3 FUTURE PERSPECTIVES

In life course epidemiology, long-term associations of early life exposures and adult health outcomes are often observed. The next step would be to clarify and quantify potential mechanisms that explain these life course associations. In this thesis, we have found associations of parental, birth, and early adult characteristics with risks of endometriosis and PDs. However, we were not able to fully identify their potential mechanistic pathways or accumulation of risks from factors operating in different life stages, which may be helpful for understanding the underlying etiology or targeting earlier interventions.

There are several questions that need to be addressed by further research. First, in Studies I and II we observed an inverse association between fetal growth rate and risk of endometriosis, which cannot be fully explained by familial confounding factors. We thus wonder whether there are mechanisms through adult factors, such as BMI or hormone levels. A previous study showed that endometriosis was more prevalent among women with lower weight in adolescence and early adulthood, which is contradictory to its estrogen-dependent disease pathology.[166] It would thus be informative to examine whether and to what extent

lower adult BMI could mediate the adverse effect from low weight or slow growth during the prenatal period, and whether there may be an interaction effect between weight at birth and in early adulthood on hormonal levels in adulthood.

Furthermore, in Study II we found that maternal smoking during early pregnancy was associated with an elevated risk of endometriosis. There was also evidence showing that exposure to passive smoking in childhood may possibly increase the risk of endometriosis.[132] Considering that mother's smoking behavior during pregnancy might imply parental smoking in one's childhood, it is still unknow whether the adverse effect on endometriosis is from fetal programming or a postnatal environmental effect. If both are possible, it is worth to further explore the sensitive period when environmental toxicant exposures exert strongest effects on the development of endometriosis.

Moreover, Study III showed that women with endometriosis were at an increased risk for several mental disorders, such as depression, anxiety and stress-related disorders, and alcohol/drug dependence. Among many other factors, e.g., familial susceptibility and immune-system dysregulation, it is plausible that these mental distresses are caused by the adverse consequences of endometriosis, such as chronic pelvic pain and subfertility. Therefore, a primary goal for future research is to explore the potential mechanism explaining associations between endometriosis and psychiatric disorders, which could help to identify high-risk groups for targeted prevention and management of mental disorders among women with endometriosis.

Additionally, it is worthwhile to emphasize and thoroughly investigate the social determinants of endometriosis and PDs, such as their associations with social mobility; and to try to detect sensitive periods in which socioeconomic position may create the gradient in ill-health. These social determinants might be important underlying contributing factors of the predictors observed in our studies, such as maternal smoking during pregnancy, stress related disorders, or alcohol/drug dependence. Research into the upstream determinants can thus provide important clues to prevent the reproduction of health inequalities over the life course and across generations.

It should also be noted that, our measures of women's socioeconomic position were mainly based on education and income. Previous studies have argued that these may not be the best predictors when assessing social inequalities in health among women.[167,168] It could be that other aspects of social inequality in women remain uncovered by these one-dimensional measures, thus leading to residual confounding. Future research with available data could consider exploring the social patterning of these female disorders with additional measures such as general social advantage (e.g., income) in the household or partner's social class.[167,169,170]

Last yet important, this thesis has demonstrated a positive association between birth weight and risk of menopausal and climacteric status, although mechanisms explaining this association remain uncertain. More research is required to investigate the potential

mechanistic pathways through, for example, adult BMI and hormone levels. Further exploring whether our observed association may vary with women's menopausal status could also shed light on the etiology of PDs and identify targets for intervention.

# 8 CONCLUSION

This thesis has found associations of maternal smoking during pregnancy and slow fetal growth rate with endometriosis, and of high birth weight with menopausal and climacterics states. The findings from this thesis support the developmental adaptation mechanism with respect to these female hormone-driven disorders. During a critical or sensitive period of life, exposure to environmental insults, such as toxic components and undernutrition, may permanently alter the programming of body structure, physiology, and metabolism,[17] which in turn makes some women more susceptible to develop certain diseases/disorders.

From a methodological perspective, this thesis demonstrated the value of combining large register-based population studies with family-based study designs for identification and quantification of residual genetic and shared (familial) environmental confounding in adult disorders with early life origins.

As also shown in this thesis, disorders during women's reproductive and perimenopausal period were associated with a range of socioeconomic, demographic, and mental factors operating in the early life stages and across generations. These factors likely exert a chain of cumulative influences on observed inequalities in health, with social factors as the upstream determinants.

Taken together, this thesis highlights the need to bring a life course perspective into research on women's health outcomes. This could help to better identify the groups of women who are particularly at risk and might also guide prevention strategies and disease management. It should be noted that the developmental origins of health and disease (DOHaD) effect is not only a biological issue but also a public health issue. To prevent adverse health outcomes that originate from early life, joint efforts - with consideration of downstream effects of social inequalities - are needed from various stakeholders, including policy makers, health professionals, researchers, as well as families and caregivers.

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